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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/483,184	01/14/2000	Ruth W. Craig	DART1110-1	8067

7590 07/24/2003

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1642	16

DATE MAILED: 07/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/483,184	Craig et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *1-5* is/are allowed.

6) ☒ Claim(s) *6-10, 14, and 16-21* is/are rejected.

7) ☒ Claim(s) *11-13 and 15* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☒ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☒ Interview Summary (PTO-413) Paper No(s). *15*
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*

DETAILED ACTION

1. Claim 10 has been amended. Claims 1-21 are pending and under consideration

2. After review and reconsideration, the finality of the Office action of Paper No. 14 has been withdrawn.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

4. The rejection of claims 1-9 under 35 U.S.C. 101 and 112, first paragraph, because the claimed invention is not supported by either a specific, substantial asserted utility or a well established utility, is withdrawn in light of applicants arguments.

5. The specification is objected to as not complying with 1.821(d) of the Sequence Rules and Regulations. Page 70 contains sequence disclosures for Bax and Bcl-2 proteins and nucleic acids that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Appropriate correction is required.

6. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

7.The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 20 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The reference to "said polynucleotide" in lines 9 and 11 of claim 20 lacks antecedent basis within the claim.

9. Claims 6-9 and 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for isolated vectors and isolated host cells for use in vitro and ex vivo, does not reasonably provide enablement for vectors or host cells comprised within an animal having undergone gene transfer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. On page 35, line 15 to page 37, line 25, the specificaition contemplates the use of expression vectors such as adenoviraus and retrovirus for gene transfer into mammalian cells. The specification is not enabling for this method of using for the follwing reasons.

The instant specification does not teach how to overcome problems with in vivo delivery and expression with respect to the administration of the claimed nucleic acids or viral vectors comprising said nucleic acids. The state of the art as of the priority date sought for the instant application is that in vivo gene delivery is not well developed and is highly unpredictable. For instance Verma et al (Nature, 1997, Vol. 389, pp. 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression (page 239, column 3). Eck et al (Gene-Based Therapy, In: The Pharmacological Basis of Therapeutics, Goodman and Gilman, Ed.s, 1996, pp. 77-101) teach that the fate of the DNA vector itself with regard to the volume of distribution, rate of clearance into tissues etc., the in vivo consequences of altered gene

expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA the level of mRNA produced, the stability of the mRNA produced in vivo, the amount and stability of the protein produced and the proteins compartmentalization or secretory fate within the cell are primary considerations regarding effective therapy. Eck et al state that these factors differ dramatically on the vector used, the protein being produced, and the disease being treated (Eck et al bridging pages 81-82).

As of the priority date sought, it was well known in the art how to infect or transfect cells in vitro or ex vivo with viral vectors. However, using viral vectors to deliver DNA to an organism in vivo, or using infected or transfected cells to deliver nucleic acids which encode a particular protein sequence to an organism in vivo is in the realm of gene therapy, and as of the priority date sought, highly unpredictable in view of the complexity of in vivo systems. Orkin et al state ("Report and Recommendation of the Panel to Assess the NIH Investment in Research on Gene Therapy", NIH, 1995) clinical efficacy had not been definitively demonstrated with any gene therapy protocol (page 1, second paragraph). Orkin et al defines gene therapy as the transfer of DNA into recipient cells either ex vivo or in vivo (page 7, under the heading "Gene transfer"), thus encompassing the instant claims drawn to the administration of antigen presenting cells transfected or infected ex vivo. Orkin et al concludes that, "none of the available vector systems is entirely satisfactory, and many f the perceived advantages of vector systems have not been experimentally validated. Until progress is made in thee areas, slow and erratic success in applying gene transfer methods to patients can be expected" Orkin et al comment that direct administration of DNA or DNA in liposomes is not well developed and hindered by the low efficiency of gene transfer (page 8, paragraph 5). Orkin et al teach that adequate expression of the transferred genes is essential for therapy, but that current data regarding the level and consistency of expression of transferred genes in animal models was unknown. Orkin et al states that in protocols not involving ex vivo infections/transfection, it is necessary to target the

expression of the transferred genes to the appropriate tissue or cell type by means of regulatory sequences in gene transfer vectors. The specification does not teach a vector having a specific regulatory sequence which would direct the expression of the nucleic acids within the appropriate tissue type.

The specification does not remedy any of the deficiencies or the prior art with regard to gene therapy. Given the lack of any guidance from the specification on any of the above issues pointed out by Verma or Eck or Orkin. One of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the methods of claims.

Amendment of the claims to recite "isolated vector" and "isolated host cell" would overcome this rejection.

10. Claims 20 and 21 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. .Claim 20 is drawn to a genus of polynucleotides which minimally hybridize to residue 2414, 2766, 3013 and 3786 of SEQ ID NO:1. The limitation of "wherein at least three nucleotides of said polynucleotide hybridize to a nucleotide sequence 5' and contiguous to said nucleotide position and 3 and wherein at least three nucleotides of said polynucleotide hybridize to a nucleotide sequence 3' and contiguous to said nucleotide position" do not further define the sequence to which the oligonucleotide is hybridizing because the language of the claim recites "a" nucleotide sequence" rather than specific residues of SEQ ID NO:1. Thus the claimed oligomers need only hybridize to "A", "G" and "C". Claim 21 is drawn to an oligomer which specifically hybridizes to residues 2412-2414 of SEQ ID NO:1 operably linked to residues 3768-3770 of SEQ ID NO:1. The conventional meaning of "operably linked" implies only that the nucletoides are in frame. There is no limitation in claim 21 for the

nucleotide 2414 of SEQ ID NO:1 to be directly linked to the nucleotide of 3768 of SEQ ID NO:1. Thus, claim 21 reads on any nucleotide sequence comprising the codon of "AAG" to be in frame with the codon " GAT". Thus, claims 20 and 21 are drawn to a genus of oligonucleotides. Numerous structural alterations are tolerated between members of the genus, as the only limitations are minimally hybridize to "A", "G" and "C" (for claim 20) and to hybridize to the codon "AAG" and "GAT" wherein the two codons are in-frame. The claimed genuses are highly variant as they comprise oligomers with widely differing structural and functional attributes. The disclosure of SEQ ID NO:1, or the polynucleotides encoding SEQ ID NO:3 do not anticipate these genuses because the genuses are highly variant. One of skill in the art would conclude that applicant did not describe an adequate number of species to describe the claimed genuses and therefore was not in possession of the invention.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 20 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by Kozopas et al (PNAS, 1993, Vol. 90, pp. 3516-3520) as evidenced by Accession Number L08248. Claim 20 is drawn in part to an oligonucleotide comprising at least ten nucleotides that hybridize specifically to a nucleotide sequence of SEQ ID NO:1 selected from the group consisting of a nucleotide sequence comprising nucleotide position 2414 of SEQ ID NO:1; a nucleotide sequence comprising nucleotide position 2766 of SEQ ID NO:1; a nucleotide sequence comprising nucleotide position 3013 of SEQ ID NO:1; a nucleotide sequence comprising nucleotide position 3786 of SEQ ID NO:1, wherein at least three nucleotide of said

polynucleotide hybridize to a nucleotide sequence 5' and contiguous to said nucleotide position, and wherein at least three nucleotide of said polynucleotide hybridize to a nucleotide sequence 3' and contiguous to said nucleotide position, or an oligonucleotide complementary thereto. Claim 21 is drawn in part to an oligonucleotide comprising at least ten nucleotides that specifically hybridize to the nucleotide sequence of SEQ ID NO:1 comprising nucletoides 2412-2414 of SEQ ID NO:1 operatively linked to nucletoides 3768-3770 of SEQ ID NO:1. When given the broadest reasonable interpretation, the claims read on a nucleotide sequence comprising a single nucleotide at positions 2414, 2766, 3013 and 3786. Further it is noted that claim 20 was rejected under 112, second paragraph, as it was unclear what "said polynucleotide" referred to in the context of the claim. When given the broadest reasonable interpretation, claim 21 reads on a nucleotide minimally comprising the three nucleotides of 2412, 2413 and 2414 of SEQ ID NO:1 operably linked with the three nucleotide of 3768, 3769 and 3770 of SEQ ID NO:1. The conventional meaning of "operably linked" implies only that the nucletoides are in frame. There is no limitation in claim 21 for the nucleotide 2414 of SEQ ID NO:1 to be directly linked to the nucleotide of 3768 of SEQ ID NO:1. Thus, claim 21 reads on any nucleotide sequence comprising the codon of "AAG" to be in frame with the codon " GAT".

Accession number L08246 discloses the mRNA for the Mcl-1 protein. An alignment of this sequence with the instant genomic sequence of SEQ ID NO:1 indicates that residues 1727-2414 of SEQ ID NO:1 are identical to residues 61-748 of L08248; residues 2766-3013 of SEQ ID NO:1 are identical to residues 749-996 of L08248; and residues 3768-3884 of SEQ ID NO:1 are identical to residues 997-113 of L08248. The complementary strand of which would hybridize to a nucleotide sequence comprising residue 2414, 3013 and 3884 of SEQ ID NO:1, and comprise at least three contiguous nucleotides both 5' and 3' to the nucletoides at residues 748, 996 and 113 of L08248. The disclosure of Kozopas et al also fulfills the limitations of claim 21 because the claim does not specify that residue 2412-2414 be directly bond to residues 3768-3770.

13. Claims 10, 14, 20 and 21 are rejected under 35 U.S.C. 102(b) as being anticipated by The New England Biolabs Catalog (1993-1994, page 91) discloses random hexamers which are complementary to the polynucleotides encoding an Mcl-1 polypeptide or the Mcl-1s/deltaTM sequence., in addition to the nucleotide position comprising nucleotide position 2414, 2766, 3013 and 3786 of SEQ ID NO:1 and the nucleotides 2412-2414 of SEQ ID NO:1 operably linked to nucleotides 3768-3770 of SEQ ID NO:1. It is noted that claims 20 and 21 do not specify that the "oligonucleotide complementary thereto" must comprise at least ten nucleotides.

14. Claims 11-13 and 15 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

15. All other rejections and objections as set forth in Paper No. 14 are withdrawn.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

July 16, 2003